IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Bruce Joseph ROSER

Serial No.: 09/888,734

Filing Date: 25 June 2001

For: DRIED BLOOD FACTOR COMPOSITION COMPRISING TREHALOSE

Examiner: Francisco Chandler Prats

Group Art Unit: 1651

Declaration of Sam L Helgerson

under 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Sam L Helgerson, declare as follows:

1. I am the same Sam L. Helgerson who is a co-inventor for US patent No.5,824,780 (Curtis *et al*). I have been with the Baxter Healthcare Corporation since 1991 and have worked during that time as a Research Scientist on projects to develop protein-based biotherapeutic products. I am now Senior Research Director in the Baxter BioScience R&D Group.

2. I have reviewed the Office Action mailed September 1, 2004 and I note the comments on page 6 stating that "the proteins (i.e., native Factor VIII and activated Factor VIII) possess numerous virtually identical amino acid sequences." However, although Factor VIIIa shares all of its amino acid sequence with Factor VIII, the two are in fact significantly different from one another in several key structural and functional aspects a was stated in the Background section of Patent 5,824,780: "Recent advances in the isolation of Factor VIII and the molecular cloning of the Factor VIII gene have revealed that the primary structure of Factor VIII contains several distinct types of structural domains. There are three A domains, A1, A2, and A3 each of approximately 350 amino acids, a unique region of about 980 amino acids called the B domain, and a carboxyl-terminal region of about 300 amino acids

called the C1-C2 domain. These domains are arranged in human Factor VIII in the order of A1-A2-B-A3C1-C2 (Vehar et al. Nature 312:327 to 342, 1984). Treatment of procoagulant protein Factor VIII with thrombin results in an increase in coagulant activity, which is associated with the formation of an activated form of Factor VIII. Previous attempts to isolate and characterize the activated form of human Factor VIII have been unsuccessful because the activity of this form rapidly decays. The activation of Factor VIII by thrombin has been shown to coincide with cleavage of the polypeptide chain at residue position 372 between the A1 and A2 domains, at position 740 between the A2 and B domains, at unidentified positions within the B domain, and at position 1689 between the B and A3-C1-C2 domains. The active Factor VIII complex then forms as a heterotrimer composed of the A1, A2, and A3-C1-C2 subunits." Hence, both the gross molecular sizes and the intramolecular subunit interactions of the two proteins are very different. Importantly, the activation of FVIII to FVIIIa is required in order to achieve the fully functional properties required for blood coagulation activity.

3. Page 6 of the office action also states that "at the very least, Curtis establishes generally that Factor VIII has a therapeutic utility that can be preserved upon freeze-drying in the presence of trehalose." I believe that this may overstate the utility of our work. In the Curtis *et al* patent (on which, as noted above, I was a co-inventor), we focused the disclosure to methods and formulations for stabilising the final activated Factor VIII protein, in other words Factor VIIIa. The protein structure of FVIIIa required for functional blood coagulation activity is highly dependent on specific intramolecular subunit interactions that are unique to FVIIIa in comparison to FVIII. In particular, these subunit interactions are very labile and must be stabilized in order for the desired activity to be maintained. Our work with protein stabilizing agents, i.e., human serum albumin, sucrose, and trehalose, was aimed specifically at solving this problem. We did not seek to extend the teaching of the patent disclosure to unactivated Factor VIII, in other words simply "Factor VIII". I believe that a person working in this field would have duly noted this and would not have assumed that the patent was teaching methods and formulations for stabilising Factor VIII. Because the two protein forms are so different from one another, the attributes of, uses of, and techniques involving one may not simply extrapolated to the other.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Fremont, CA, on 30 November 2004.

(city) (state) (day)

Sam S. Halgerson
(name)